IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Hermann P.T. AMMON et al.	Group Art Unit: 1623
Application No.: 09/011,977	Examiner: Howard V. Owens, Jr.
Filed: June 15, 1998	Confirmation No.: 1580
For: USE OF BOSWELLIC ACID AND ITS DERIVATIVES FOR INHIBITING NORMAL AND INCREASED LEUCOCYTIC ELASTASE OR PLASMIN ACTIVITY	

REPLY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In complete response to the Office Action mailed September 9, 2003, Applicants submit the following remarks.

As correctly stated in the Official Action, Claims 10, 12-16, 18-22, 24, 25, and 27-40 are pending in the present application. Claims 10, 12-16, 18-22, 24, 25, and 27-40 stand rejected.

Request for Interview

In light of the length of pendency of the above-identified application, Applicants respectfully request an interview with the Examiner and the Examiner's supervisor **prior to issuance of the next Official Communication**. This is a repeat of the request submitted with Applicants Request for Continued Examination filed June 25, 2003. However, should the amendments and arguments contained in this

Reply & Amendment put the application in consideration for allowance, such an interview is, of course, unnecessary. A separate Request for Interview is submitted herewith.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 10, 12-16, 18-22, 24, 25, and 27-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. The Office Action suggests that the specification does not support the treatment of the destruction of functional tissue in vivo, but rather only the inhibition of human leucocytic elastase (HLE) *in vitro*. This rejection is respectfully traversed.

The Office Action points to the Bernstein et al. publication (Progress in Medicinal Chemistry 31:59-120 (1994)) as an indication that *in vitro* inhibition of HLE does not adequately support *in vivo* treatment. Applicants note that the Advisory Action contained a similar assertion. Applicants addressed this assertion fully in the Remarks section of the Request for Continued Examination submitted on June 25, 2003. However, the present Office Action does not rebut any of Applicants' arguments or address why such arguments are not persuasive to overcome the rejection. (In light of this failure, Applicants respectfully submit that should the Examiner insist on maintaining such a rejection, the next Action **should not be made final** as the Examiner has not provided any new particular technical arguments for Applicants to adequately address).

Applicants respectfully maintain that the Office Action does not accurately apply the standard for enablement. Enablement does not require an absolute guarantee that an particular invention will work *in vivo*, if it is shown to work *in vitro*.

The standard for enablement for chemical/pharmaceutical inventions is discussed in M.P.E.P. §2164.02:

> If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against the correlation and decide whether one skilled in the art would accept the model as reasonably correlated to the condition. *In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Withdrawal of this rejection is respectfully requested.... A rigorous or invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

M.P.E.P. §2164.02.

Thus, a simple statement in the Bernstein reference that *in vitro* activity does not always produce corresponding *in vivo* activity does not nullify the enablement of the presently claimed invention. In fact, Bernstein et al. still accept the general proposition that a compound that inhibits HLE *in vitro* will likely elicit *in vivo* inhibition. Bernstein et al. further cite the Bieth reference on page 65 as helping to further predict which compounds are likely to elicit *in vivo* inhibition based on standard enzyme kinetics. Accordingly, the skilled artisan **does accept that *in vitro* inhibition of HLE corresponds to *in vivo* inhibition**. The fact that any compound or composition may be inactivated, excreted, etc. before causing its intended effect does not render the use of the claimed compound or composition not enabled. The courts have never required an exhaustive study of *in vivo* pharmacokinetics/pharmacodynamics for a finding of enablement. This would

appear to be especially true when techniques to determine such effects are well known in the art, as in the present case. The statement by Bernstein et al. is nothing more than a standard disclaimer stating that some compounds may have a slow enough rate of inhibition that they are inactivated before they can take effect. Bernstein et al. do not state that many or most *in vitro* HLE inhibitors are likely to be ineffective *in vivo*. Interestingly, Bernstein et al. point out (on page 65) that even slow inhibitors of HLE have been shown to be efficacious.

Bernstein et al. and the present specification (*see, e.g.*, pages 5-6) both describe the well-known destructive nature of HLE on tissue. In fact, the specification indicates that selective inhibitors of HLE were unavailable for use, which prevented the skilled artisan from effectively treating the destruction of functional tissue prior to the presently claimed invention. The present specification demonstrates that boswellic acid derivatives are capable of selectively inhibiting HLE *in vitro*. Accordingly, in light of the current case law, Applicants respectfully submit that such evidence is sufficient to support enablement for the use of these compounds *in vivo* to treat the destruction of functional tissue as in the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 10, 12-16, 18-22, 24, 25, and 27-40 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Ammon et al. (EP 0 552 657) in view of Mulshine et al. (WO 95/24894) and Han (Chin. Med. Sci. J. 9(1):61-69). The Office Action asserts that Ammon et al. recognizes that boswellic acid can be used for prophylaxis or control of inflammatory processes caused by elevated leukotriene formation. The

Examiner asserts that Ammon et al. disclose the use of boswellic acid for treatment of inflammatory conditions of the joints, bronchitis, chronic hepatitis, and chronic asthma. The Examiner concludes that Ammon et al. recognize the use of boswellic acid to treat the same conditions as the presently claimed invention. Mulshine et al. allegedly indicate the efficacy of 5-lipoxygenase inhibitors in the treatment of cancer. Han allegedly supports the usefulness of boswellic acid derivatives in the treatment of cancer. This rejection is respectfully traversed.

Applicants initially note that page 4 of the Office Action mistakenly recites a summary of earlier pending claims in the present application and does not appear to take into account the current language of the claims, including the amendments made in the Request for Continued Examination filed on June 25, 2003. In particular, neither "chronic bronchitis" nor "hepatitis" appears in Claim 10. "Hepatitis" does not appear in independent Claim 28. Moreover, independent Claim 29 is not drawn to a method of treating cancer, but to a method for treating the destruction of functional tissue associated with tumors, neoplasms, or tumor metastases.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that the cited publications do not disclose or suggest all of the claim limitations nor provide a reasonable expectation of success.

The present invention is drawn to **methods of combating severe diseases**, such as pulmonary emphysema, acute respiratory distress syndrome, shock lung,

cystic fibrosis, glomerulonephritis, and rheumatoid arthritis (independent Claim 10) and **to treating functional tissue damage** associated with pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis (mucoviscidosis), chronic bronchitis, glomerulonephritis, and rheumatoid arthritis (independent Claim 28) and tumors, neoplasms, or tumor metastases (independent Claim 29) caused by increased leucocytic elastase or plasmin activity. The diseases to be treated by the present invention are characterized by damage to functional tissue caused by release of leucocytic elastase. The methods of the present invention comprise administering an effective amount of boswellic acid, a physiologically acceptable salt, a derivative, a salt of the derivative, a plant extract containing boswellic acid, or combinations thereof.

As noted in the specification, the inhibition of leucocytic elastase is important because, during the pathophysiological processes of the diseases being treated, this enzyme (which is released from activated neutrophilic granulocytes) plays an important part in the destruction of functional tissue. Thus, the aim of the present invention is to block the final destruction of tissues and organs resulting from the indicated diseases. Until Applicants discovered that boswellic acid inhibits leucocytic elastase, it was not known that boswellic acid could be used for such a purpose.

In contrast, in the prior art, 5-lipoxygenase inhibitors, such as boswellic acids, had only been claimed to be useful for treating **mild to moderate diseases**, such as asthma. There was no indication in the prior art that 5-lipoxygenase inhibitors could be used to treat more severe diseases, such as those treated by the present invention. Thus, there was no reasonable expectation of success.

Ammon et al. disclose the use of boswellic acid compounds for treating inflammation in some diseases by inhibiting leukotriene synthesis. Although Ammon et al. lists among the diseases to be treated "diseases of the joints (rheumatism)," Applicants note that rheumatoid arthritis (which is treated by the present invention) is very different from other rheumatoid diseases. Rheumatoid arthritis is based on the destruction of the articular cartilage, in contrast to other rheumatoid diseases. This destruction leads to an irreversible deformation of the joint which hinders movement. The destruction of the articular cartilage is not prevented by other drugs for the treatment of rheumatoid arthritis, such as inhibitors of cyclooxygenase or 5-lipoxygenase. Thus, rheumatoid arthritis is a very different disease than rheumatism, and cannot be treated by similar drugs. Applicants further note that Claim 10, as amended, does not recite any of the same diseases discussed in the Ammon et al. publication, but rather recites more serious diseases that can be treated by inhibiting human leucocytic elastase. (Applicants note that the Examiner's statement on page 5 of the Office Action, last paragraph, regarding the scope of Claim 10 is incorrect in this regard.) Thus, Ammon et al. do not disclose or suggest all of the limitations of the presently claimed invention.

Thus, although Ammon et al. may disclose the use of boswellic acid for influencing inflammation, such a disclosure would not suggest the present invention, which uses boswellic acid for combating more serious diseases and conditions caused by an increase in leucocytic elastase activity. While there could be an inflammatory component to some of the diseases recited in the present claims (pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis (mucoviscidosis), glomerulonephritis, and rheumatoid arthritis) caused by the

destruction of functional tissue that occurs, this does not mean that one skilled in the art would treat these diseases with anti-inflammatory compounds, particularly boswellic acid. The Examiner's argument is akin to implying that one can effectively treat cystic fibrosis with aspirin, another anti-inflammatory compound. Such a treatment regimen would not be efficacious. Similarly, because boswellic acid was known to inhibit 5-lipoxygenase, this would not lead one skilled in the art to believe that this compound can be used to treat severe diseases such as that claimed. Accordingly, there is no reasonable expectation of success in treating the severe diseases claimed with a simple anti-inflammatory compound, much less boswellic acid. If the Examiner maintains this position, Applicants respectfully request that the Examiner provide documentary evidence or an Examiner's affidavit to this effect, rather than a broad conclusory statement.

The Office Action implies that Applicants have admitted that "the prior art has recognized the ability of the pentacyclic triterpene class of compounds, of which Boswellic acid is a member, (p. 3, lines 14-21) to inhibit human leucocytic elastase (HLE)." This statement is much broader than what is disclosed in the cited portion of the specification. The specification indicates the "inhibition of human leucocytic elastase by **some** pentacyclic triterpene derivatives was shown." (emphasis added). This is **not** an admission that pentacylic triterpenes as a class inhibit HLE, as suggested by the Office Action. To the contrary, Applicants respectfully submit that because some pentacyclic triterpenes were known to inhibit HLE, this is not sufficient to lead the skilled artisan to believe that all pentacyclic triterpenes do so. The Ying et al. publication cited in the specification on page 3 only tested several pentacyclic triterpenes, which were found to have a range of activity toward this enzyme; *i.e.*,

some possessed poor Ki values. Applicants previously submitted, as Exhibit A, with the response filed April 29, 2003, a review article (J. Patocka, *J. Appl. Biomed.* 1:7-12 (2003)). This article notes that there are at least 4000 known triterpenes, with a wide spectrum of biological activities. *See* abstract. Some triterpenes inhibit HLE effectively, but many do not. Thus, one skilled in the art would not reasonably conclude that boswellic acid would inhibit HLE, nor would be motivated to select boswellic acid out of the numerous pentacyclic triterpenes known. Further, there is no known correlation of inhibition of 5-lipoxygenase with HLE inhibition. Therefore, it does not follow from the Examiner's statement that the art recognizes the efficacy of 5-lipoxygenase inhibitors to treat cancer or inflammatory conditions, that the art would recognize that boswellic acid could be used to treat severe inflammatory diseases (independent Claim 10) or to treat the destruction of functional tissue (independent Claims 28 and 29) by inhibiting HLE, as in the presently claimed invention.

Mulshine et al. discloses that lipoxygenase inhibitors, i.e., inhibitors of 5-lipoxygenase, can be used to treat epithelial cell-derived cancer. Mulshine et al. provide evidence that three different 5-lipoxygenase inhibitors exert cytotoxic actions in tumor cells. There is not suggestion that other inhibitors of 5-lipoxygenase, such as boswellic acid, would have the same effect. Nor does Mulshine et al. disclose or suggest that boswellic acid could be used to treat the destruction of functional tissue via the inhibition of HLE, as in the presently claimed invention. Han also does not disclose or suggest the use of boswellic acid to treat the destruction of functional tissue by inhibiting HLE.

In summary, Ammon et al. do not disclose or suggest that the severe inflammatory diseases recited in the presently claimed invention can be treated with boswellic acid. Moreover, neither Ammon et al. nor the Han or Mulshine et al. publications disclose or suggest that boswellic acid could be used to inhibit human leucocytic elastase to treat the destruction of functional tissue associated with certain diseases, tumors, neoplasms, and tumor metastases. It was not until the present inventors discovered that boswellic acid could inhibit HLE that the presently claimed invention was possible. Accordingly, the cited publications do not disclose or suggest all of the claimed limitations.

The Examiner argues that Applicants' connection of boswellic acid to leucocytic elastase or plasmin activity is considered to be discovery of one of the pathways affected by boswellic acid and that such does not obviate the use of boswellic acid to treat inflammatory conditions, neoplasms, or cancer. *See* Office Action, p. 5. Thus, the Examiner appears to suggest that the inhibition of HLE is simply an inherent property of boswellic acid. Applicants respectfully submit that the Examiner has misapplied the standard regarding inherency and obviousness. Inherency and obviousness are not synonymous. *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966). If the skilled artisan does not recognize or appreciate an inherent result, it cannot be obvious. *In re Naylor*, 152 U.S.P.Q. 106, 108 (C.C.P.A. 1966); *In re Shetty*, 195 U.S.P.Q. 753, 756 (C.C.P.A. 1977). "Obviousness cannot be predicated on what is unknown." *Sporman* at 452. *See also In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993) (reinforcing the holding of *Spormann*). Until the presently claimed invention, one skilled in the art would not have appreciated that boswellic acid inhibited HLE and thus could be used for the treatment of the

destruction of functional tissue. The skilled artisan must have recognized or appreciated the particular property claimed in the present invention. Applicants have provided evidence above that this was not the case. Thus, the cited publications cannot render the presently claimed invention obvious.

Withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: March 9, 2004

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